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Antimicrobial resistance profile of methicillin resistant staphylococcal aureus from skin and soft tissue isolates

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Original Article

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Abstract

Objectives: To evaluate resistance rates in methicillin resistant Staphylococcus aureus (MRSA) against clindamycin, cotrimoxazole, tetracycline, fusidic acid, rifampicin and chloramphenicol isolated from skin and soft tissue infections (SSTI).

Methods: Descriptive analysis of SSTI samples yielding MRSA in clinical laboratory of a tertiary care center; receiving specimens across Pakistan from January 2005 to June 2007.

Microbiological Methods: MRSA were identified using standard microbiological techniques. Susceptibility testing was performed by disc diffusion according to Clinical Laboratory Standards Institute (CLSI) against fusidic acid, tetracycline, cotrimoxazole, clindamycin, rifampicin and chloramphenicol. Minimum inhibitory concentrations (MIC) of rifampicin were determined using agar dilution method according to CLSI.

Results: During the study period 501 MRSA were isolated from SSTI. Overall variable susceptibility pattern with high resistance rates to tetracycline (82%), clindamycin (79%), cotrimoxazole (59%), and rifampicin (50%) were observed. Resistance to chloramphenicol (10%) and fusidic acid (9%) was low.

Conclusion: There is a strong need in resource limited countries to review the utility of conventional antibiotics for the management of MRSA SSTI as new agents are expensive and not available. High resistance rates were observed against cotrimoxazole, tetracycline and clindamycin. Resistance to fusidic acid, rifampicin and Chloramphenicol was low (JPMA 59:266; 2009).

Introduction

Staphylococcus aureus causes skin and soft-tissue infections (SSTIs) that range from folliculitis to life-threatening conditions, such as necrotizing fasciitis.[1] Emerging methicillin resistance among Staphylococcus aureus initially in nosocomial and recently in community isolates is problematic because empirical choice of antimicrobials must include agents with activity against resistant strains.[2] Management of MRSA infections is challenging as these strains are resistant to all beta lactam antibiotics. In contrast to health care associated MRSA isolates that are resistant to multiple antibiotics, community-associated MRSA isolates tend to be resistant to fewer antibiotics and often remain susceptible to non-beta lactam antibiotics, such as clindamycin, sulfonamides, and tetracyclines.[1,2]

Vancomycin has excellent efficacy in skin and soft-tissue infections in general and specifically against those due to MRSA.[3] However, for various reasons these agents should be reserved for patients who have severe infections requiring hospitalization or who have not responded to attempts to eradicate the infection. Firstly, excessive use of vancomycin would result in emergence of vancomycin resistance.[2,3] Secondly, vancomycin is expensive and available only in parenteral form and most of the times its administration requires hospitalization.[3] Finally, it is a nephrotoxic drug and requires monitoring of renal function and drug levels that lead to increased morbidity and costs for the patient.

Alternate options for the MRSA infections include newer agents like linezolid, daptomycin, tigecycline, and quinupristin/dalfopristin.[3] However, these agents are either very expensive or not available in Pakistan.[3] Guidelines for the treatment of skin and soft tissue infections published by CDC in 2005 have also recommended the use of macrolides, clindamycin, trimethoprim-sulfamethoxazole, tetracycline, doxycycline or minocycline in minor MRSA infections.[4]

In addition, many studies from different regions of the world have reported efficacy of fusidic acid, rifampicin, clindamycin, tetracycline, cotrimoxazole and chloramphenicol in skin and soft tissue infections with MRSA.[5,6] All of these antibiotics are potent antistaphylococcal agents with good tissue penetration, cheaper as compared to glycopeptides and are also available in both oral and parenteral formulations.[4] However, their use is limited in developed countries due to their potential adverse effects.

There is a strong need in resource limited countries like Pakistan to review the utility of conventional antibiotics effective for the management of skin and soft tissue infections caused by MRSA. However, published data in Pakistan is

limited in this regard. Therefore, this study was conducted to explore the cheaper and easy to administer drugs for soft tissue infections by MRSA. The susceptibility pattern of MRSA strains were evaluated against fusidic acid, cotrimoxazole, rifampicin, chloramphenicol, clindamycin and tetracycline isolated from SSTIs. Moreover, studies from Pakistan that reported susceptibility pattern of MRSA were reviewed and their findings were correlated with our results.

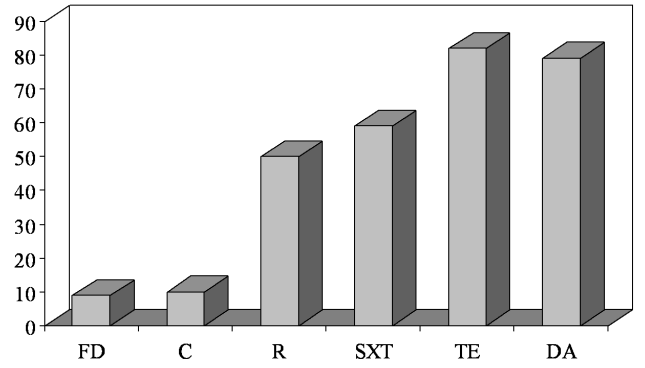
Material and Methods

This study was conducted at the Clinical Microbiology Laboratory of Aga Khan University Hospital that receives specimens from across Pakistan via its collection points. Skin and soft tissue samples yielding growth of S.aureus from January 2005 to June 2007 were included. Organisms were identified as S.aureus by Gram stain, catalase and coagulase test.[7] Other supplemental tests were DNAse, phosphatase and mannitol fermentation.[7] Antimicrobial sensitivities against oxacillin (1 g), fusidic acid (10 g), cotrimoxazole (30µg), tetracycline (30µg), clindamycin (2µg) and chloramphenicol (25 µg) were performed by Kirby Bauer method according to Clinical Laboratory Standards Institute (CLSI).[8] Methicillin resistance was confirmed by oxacillin screen agar containing 6 g/ml oxacillin and incubation at 30 C for 24 hours.[8] Sensitivities against rifampicin were determined by minimum inhibitory concentration (MIC) method using agar dilution according to CLSI.[8]

Literature review was done using Pubmed, google, medscape and Pakmedinet using different terms "MRSA and susceptibility pattern", "MRSA and skin and soft tissue" etc. All the information was recorded on a standard questionnaire.

Results

During the study period a total of 501 MRSA strains were isolated from skin and soft tissue specimens. Overall, variable susceptibility pattern was observed in MRSA strains, with high resistance rates to tetracycline (TE) (82%), clindamycin (DA) (79%), cotrimoxazole (SXT) (59%), and rifampicin (R) (50%). Resistance to chloramphenicol (C) (10%) and fusidic acid (FA) (9%) was low (Figure).



(FD= Fusidic acid, 10µg; C=Chloramphenicol, 25µg; R=Rifampicin; TE= Tetracycline, 30µg; SXT= Cotrimoxazole, 30µg; DA= Clindamycin, 2µg)

Figure: Resistance pattern of MRSA.

Analysis of data from the studies done in various regions of Pakistan is shown in Table.

Discussion

Increasing antimicrobial resistance has emerged globally as one of the paramount microbial threats of the 21st century.[9] Infections due to MRSA are the significant cause of morbidity and mortality worldwide. Incidence of MRSA is increasing worldwide, and is escalating in Pakistan.[10-13] Previously MRSA infections were a concern only in hospitals but now MRSA is isolated frequently from the infections acquired in the community.[14] Skin and soft tissue infections are the major manifestations of community-acquired MRSA strains. During the past 15 years emergence and dissemination of these strains had led to major therapeutic and infection control related problems.

Methicillin resistance in Staphylococcus aureus restricts therapeutic options for clinical isolates; especially those isolated from SSTIs. Alternative treatment options include fusidic acid, cotrimoxazole, clindamycin, tetracycline, rifampicin, quinolones, and chloramphenicol.

Table: Percentage resistance in MRSA isolates reported in various studies from Pakistan.

Setting	No. of MRSA Isolates	TE	C	DA	SXT	FD	RIF	Reference
Lahore								
2003-2005	307	100	-	37	96	-	5	J Hosp Infect[23]
Rawalpindi								
2003	516	51	-	70	57	-	60	Emerg Infect Dis[24]
Rawalpindi								
2001-2004	185	89	38	-	77	-	-	Pak J Med Sci[10]
Karachi								
2004-2005	82	-	-	90	-	2	-	J Pak Med Assoc[25]
Karachi								
2005-2007	501	82	10	79	59	9	50	Current study

Prediction of sensitivity to these drugs requires knowledge of antibiotic susceptibility pattern of MRSA from a particular region. Our MRSA strains from both hospital and community showed low resistance to fusidic acid that is comparable with studies reported from USA,[9,14] Australia[5] and South Africa.[15] Fusidic acid is available in intravenous, oral, and topical preparations and when given systemically is widely distributed throughout the body, including areas such as bone, joint fluid, prostate and large abscesses.[16] Therefore, it can be particularly useful in treating MRSA.[16] However, it is well recognized that use of fusidic acid, as monotherapy, is associated with increased resistance as compared to combination therapy.[16] Therefore, combination treatment with rifampicin or cotrimoxazole is advisable and proven to be beneficial in treatment and eradication of MRSA stains.[5,9] Recent studies from different parts of the world indicate increase in the usage of fusidic acid as topical monotherapy for the treatment of skin infections especially in Europe.[17] Such topical therapy has proven effective but has also been associated with significant emergence of resistance.[17] Thus, clinicians should reconsider the use of topical fusidic acid monotherapy especially for prolonged periods.

The resistance to rifampicin (50%) was relatively better as compared to other agents. Rifampicin is another oral antimicrobial agent with good tissue penetration. This agent could be used to treat MRSA infections in our setting. However, as Pakistan is a high burden Mycobacterium tuberculosis (TB) country, increased usage of rifampicin is not advisable as a routine for the management of MRSA SSTI because of potential development of resistance in TB. However, its use is justified in certain difficult clinical situations when treatment options are very limited.

We observed high resistance rates to clindamycin, tetracycline and cotrimoxazole in our MRSA isolates. A higher rate of clindamycin resistance in endemic isolates is disappointing as this drug has a very good efficacy in MRSA SSTI.[18]

Cotrimoxazole has also been used in clinical studies with a cure rate of 86-90% in MRSA SSTI[18] Likewise, tetracycline derivatives, doxycycline and minocycline also have excellent tissue penetration, and demonstrate good antistaphylococcal activity at clinically achievable levels with a reported cure rate of 83% in MRSA skin and soft tissue infections.[19] However, high resistance rates to this drug were observed in our study probably due to irrational use of this antibiotic by general practitioners in Pakistan. Another concern is the toxicity that is associated with cotrimoxazole.

Resistance to chloramphenicol was low (10%); however, its role in management of MRSA soft tissue infection is yet to be defined. There are certain trials of usage of chloramphenicol in multi-drug resistant gram-positive organisms like MRSA, vancomycin-intermediate Staphylococcal.aureus (VISA), vancomycin-resistant Staphylococcal.aureus (VRSA) and vancomycin-resistant enterococcus (VRE).[20] Chloramphenicol is routinely used for the management of VRE infections at our institute. Data for use of this antibiotic for the management of MRSA infections is limited; however, it should be reserved for cases when there are very limited therapeutic options. Further clinical trials are needed before its routine use is indicated for the treatment of MRSA infections.

In this study, all the strains showed susceptibility to vancomycin. Vancomycin is a glycopeptide and is currently a drug of choice for MRSA infections.[4] Since there is recognition of VRE, the emergence of VRSA has been anticipated in future. There are few reports of VRSA/VISA cases from US.[21] One of the common risk factor for acquiring VISA is the long-term use of vancomycin.[22] It is therefore important to consider alternate treatment options for MRSA infections to prevent the VISA/VRSA acquisition. The emergence of S.aureus with reduced susceptibility to Vancomycin presents the potential for infection with a virulent organism for which therapeutic options are severely limited.

Comparison of our study results with other published studies of Pakistan from Lahore,[23] Rawalpindi[24] and Karachi[25] revealed resistance rates against clindamycin, tetracycline and cotrimoxazole similar to our study. Likewise, rifampicin sensitivity results and fusidate sensitivity from a previous study done in Karachi[25] correlated with our findings.

Conclusion

MRSA is a major pathogen in skin and soft tissue infections worldwide. One of the limitations of this study is the lack of differentiation between hospital acquired and community associated strains. Therefore, no comments can be made on the difference in susceptibility pattern of community and hospital acquired strains. High resistance rates against cotrimoxazole, tetracycline and clindamycin were observed. Therefore, empirical therapy with these agents at our centre is not recommended; however, these agents could be used after the sensitivity results are available. Resistance to fusidic acid and rifampicin was low; however, as monotherapy with these agents could lead to resistance, therefore, combination therapy should always be used. Resistance to chloramphenicol was very low but clinical trials recommending its use in MRSA skin and soft tissue infections are limited and further evidence is required before its routine use.

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